ANNALS of Clinical and Translational Neurology
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AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Clinical and imaging predictors of late-onset GM2 gangliosidosis: A scoping review

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Received: 18 October 2023; Accepted: 3 November 2023

***Annals of Clinical and Translational Neurology* 2024; 11(1): 207–224**

doi: 10.1002/acn3.51947

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Dr. Stephen and Dr. Locascio completed the statistical analysis.

Abstract

Objective: Late-onset GM2 gangliosidosis (LOGG) subtypes late-onset Tay-Sachs (LOTS) and Sandhoff disease (LOSD) are ultra-rare neurodegenerative lysosomal storage disorders presenting with weakness, ataxia, and neuropsychiatric symptoms. Previous studies considered LOTS and LOSD clinically indistinguishable; recent studies have challenged this. We performed a scoping review to ascertain whether imaging and clinical features may differentiate these diseases. **Methods**: We examined MEDLINE/non-MEDLINE databases up to May 2022. Articles reporting brain imaging findings in genetically/enzymatically confirmed LOGG, symptom onset at age $\geq$ 10 years (or evaluated at least once $\geq$18 years) were included, yielding 170 LOGG patients (LOTS = 127, LOSD = 43) across 68 papers. We compared LOTS versus LOSD and performed regression analyses. Results were corrected for multiple comparisons. **Results**: Age of onset was lower in LOTS versus LOSD (17.9 $\pm$ 8.2 vs. 23.9 $\pm$ 14.4 years, $p = 0.017$), although disease duration was similar ($p = 0.34$). LOTS more commonly had psychosis/bipolar symptoms (35.0% vs. 9.30%, $p = 0.011$) but less frequent swallowing problems (4.10% vs. 18.60%, $p = 0.041$). Cerebellar atrophy was more common in LOTS (89.0%) versus LOSD (60.5%), $p < 0.0001$, with more severe atrophy in LOTS ($p = 0.0005$). Brainstem atrophy was documented only in LOTS (14.2%). Independent predictors of LOTS versus LOSD (odds ratio [95% confidence interval]) included the presence of psychosis/bipolar symptoms (4.95 [1.59–19.52], $p = 0.011$), no swallowing symptoms (0.16 [0.036–0.64], $p = 0.011$), and cerebellar atrophy (5.81 [2.10–17.08], $p = 0.0009$). Lower age of onset (0.96 [0.93–1.00], $p = 0.075$) and tremor (2.50 [0.94–7.43], $p = 0.078$) were marginally statistically significant but felt relevant to include in the model. **Interpretation**: These data suggest significant differences in symptomatology, disease course, and imaging findings between LOTS and LOSD.

Introduction

GM2 gangliosidoses are lysosomal storage disorders caused by mutations in the in the α- and β-subunits of β-hexosaminidase, named Tay-Sachs and Sandhoff disease, respectively, and mutations in the GM2 activator protein, GM2 activator protein deficiency. This results in neuronal damage due to accumulation of GM2-ganglioside within lysosomes and progressive neurological disease.[1] GM2 gangliosidosis subtypes have been described, based on the age of onset and disease course, although the definitions of these subtypes vary.[2] Late-onset GM2 gangliosidosis (LOGG) typically presents after age 10 and patients survive into adulthood.[2,3] LOGG are ultra-rare neurodegenerative disorders, which are slowly progressive, and distinct from the subacute juvenile subtype (normal development, with symptom onset from age 2–5 years) and the more common, severe pediatric subtype (fatal in early childhood).[2] Scant neuropathological studies demonstrate characteristic ballooned neurons.[4–7] There is a wide phenotypic spectrum, with involvement of both the central and peripheral nervous system, resulting in several core phenotypes (predominantly neuromuscular, cerebellar, or psychiatric),[8] and considerable diagnostic delays.[9] Symptoms of LOGG primarily involve ataxia from cerebellar involvement and weakness (both upper [UMN] and lower motor neuron [LMN]), with a predilection for the triceps and quadriceps, leading to early use of walking aids and functional impairment.[9] Cognitive dysfunction has been reported,[10,11] and psychiatric symptoms may be prominent.[12] Structural imaging has revealed cerebellar atrophy, even in the absence of cerebellar clinical signs[3]; however, only few studies, containing small sample sizes have assessed imaging features of LOGG.[13,14]

Previous studies, with small patient cohorts, have considered late-onset Tay-Sachs (LOTS, which is more common, and hence has received greater study) and late-onset Sandhoff disease (LOSD,) to be clinically indistinguishable.[2,15] However, recent studies have challenged this notion: LOSD appears to have a later age of symptom onset,[3] while psychiatric symptoms appear more prevalent in LOTS.[3,12,16,17] LOTS patients also frequently have a postural and kinetic tremor and may present with characteristic, stuttering speech.[18] Additionally, a study from our group supported these differences, demonstrating higher rates of ataxia and cognitive/psychiatric symptoms (attributed to the cerebellar cognitive affective syndrome[19]) in LOTS compared to LOSD.[20] Furthermore, the two populations had distinct structural imaging features: LOTS patients had considerable cerebellar volume loss, while the limited LOSD cohort had normal imaging findings.[13,20] It was, however, acknowledged that the LOSD patients all had a neuromuscular, as opposed to ataxic, phenotype.[13,20]

To further characterize differences in clinical presentation and imaging between LOTS and LOSD, we analyzed published imaging studies and corresponding descriptions of clinical characteristics in a large, combined cohort. Improving imaging and phenotypic characterization may help differentiate these two disorders at an earlier stage and highlight differences in disease pathogenesis. Such discriminating features will be relevant to forthcoming LOGG clinical trials (historically, LOTS and LOSD have been studied together in trials, in part given their extreme rarity), as pathophysiological differences may result in differential treatment effects.

Methods

Standard protocol approvals, registrations, and patient consent

This scoping review (overview of literature surrounding a broad topic) adheres to the PRISMA guidelines.[21] The PRISMA flow diagram is shown in Fig. 1. Ethical approval was waived by the MassGeneral Brigham Institutional Review Board.

Database search strategy and selection process

A systematic search of MEDLINE and non-MEDLINE databases was performed to access relevant articles published up to May 2022. Specific medical subject headings (MeSH) and text-based search terms related to GM2 gangliosidosis included: "gangliosidoses", "GM2", "G (M2)", "ganglioside metabolism", "beta-N-acetylhexosaminidases/deficiency", "GM2 gangliosidosis", "GM2 gangliosidoses", "hexosaminidase", "Tay Sachs", "Tay-Sachs", and "Sandhoff". Search terms related to age of onset included: "adult", "late-onset", "juvenile", "subacute", "chronic", "adolescent", or "atypical". References for each selected article were reviewed to find additional references that database searches may not have identified.

Inclusion criteria

Inclusion criteria were: publication in English; genetically or enzymatically confirmed LOGG; symptomatic onset at age ≥ 10 years, or seen clinically at least once at age ≥ 18 years; and a description of brain imaging, with brain magnetic resonance imaging (MRI), or computed tomography (CT) in at least one patient. Juvenile/infantile patients were excluded.

Data collected

Within each article, if some patients met the inclusion criteria and others did not, data were only extracted for patients that met all criteria. Data extracted for subjects included: sex, method of diagnosis, LOGG subtype (LOTS/LOSD), race/ethnicity (as described), age of symptom onset, initial symptoms, description of clinical findings, and details of imaging findings. Clinical findings were classified as: UMN involvement (spasticity,

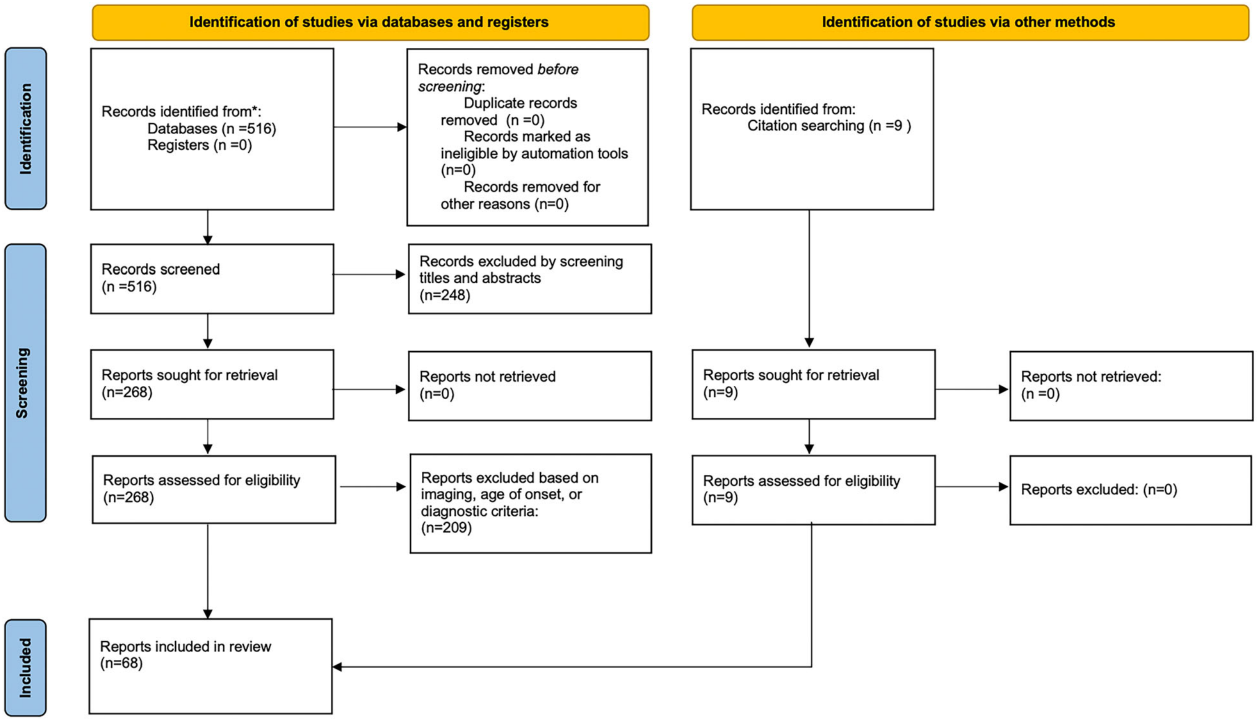

Figure 1. PRISMA flowchart for scoping review in the LOGG cohort.[21]

hyperreflexia, etc.), LMN involvement (atrophy, fasciculations, hyporeflexia, etc.), cerebellar ataxia, cognitive deficits/dementia (patient/clinician reported), psychiatric symptoms (specifically psychosis or bipolar affective disorder), speech difficulties (dysarthria, stuttering, etc.), swallowing difficulties, tremor, and other movement disorders (parkinsonism, etc.). Age of onset and age at presentation were sometimes nonspecific (using descriptive terminologies, such as adolescence, late childhood etc., or ranges) and in these cases, average ages within an age group, using either accepted World Health Organization definitions, or an average age within these ranges were used in their place. Disease duration was defined as the duration in years between age of symptom onset and age at presentation, including based on above estimated age at onset. Structural brain imaging findings were categorized as the presence of cerebellar atrophy, cerebral atrophy, brainstem atrophy, and other pertinent features. Cerebellar atrophy was further categorized if there was a specific description of severity of atrophic change (mild, moderate, and severe). If patients were described at multiple timepoints, clinical and imaging findings at the latest timepoint were used for consistency. When possible, in cases that were described in more than one article were identified, the latest assessments were used. Where MRI findings were available, these were preferentially used over CT findings.

Statistical analysis

Statistical analysis was performed using SAS (Version 9.4; SAS Institute, Cary, NC). Descriptive statistics were computed using chi-squared and Fisher's exact tests for categorical variables and *t*-tests for continuous variables. We computed Spearman correlations to determine associations of the reported degree of cerebellar atrophy (no atrophy, mild, moderate, and severe atrophy, used as an ordinal measure) to age at presentation, age at neuroimaging scan, and disease duration. We performed multivariate logistic regression analyses to determine clinical and imaging predictors significantly differentiating LOTS and LOSD. Significance level was designated as two-tailed $p < 0.05$. In all comparisons based on clinical characteristics, results were corrected for multiple comparisons using the Bonferroni method.

Results

Search results

In total, 516 citations were identified. Nine additional papers were identified through the references of articles. 525 papers were screened, and 248 were excluded. Two papers included overlapping patients,[3,22] and two had additional advanced research imaging techniques in the same cohort.[13,20] 277 articles were potentially eligible; 68 met the prespecified inclusion and exclusion criteria, yielding 170 individual LOGG patients (127 LOTS, 43 LOSD) (Table 1).

Demographics

The demographics of the LOGG cohort ($n = 170$) are shown in Table 2. The LOGG cohorts were balanced regarding sex ($p = 0.33$). Ethnicity was documented in 137 cases (33 missing), with significant differences between LOGG subtypes: in those with data, LOTS were evenly divided between non-Jewish European (49.5%) and Ashkenazi-Jewish (46.7%), while LOSD had no documented Ashkenazi-Jewish ethnicity, with the majority non-Ashkenazi-Jewish European (60.0%). Mean age of symptom onset for those with data ($n = 151$) was lower in LOTS: 17.9 ± 8.2 years versus LOSD: 23.9 ± 14.4 years ($p = 0.017$), although disease duration was similar ($p = 0.34$).

Clinical characteristics

Clinical characteristics were not reported in a single study of 4 LOTS patients, so the LOTS totals herein were $n = 123$, while all 43 LOSD patients had clinical characteristics reported. Clinical comparison between LOTS and LOSD is shown in Fig. 2A. Psychosis/bipolar symptoms were significantly more common in LOTS versus LOSD (25.0% vs. 9.3%, $p = 0.011$), while swallowing difficulties were significantly less common in LOTS (4.1% vs. 18.6%, $p = 0.041$). The presence of LMN features, UMN features, and cognitive dysfunction were similar between groups. Frequencies of ataxia (LOTS: 76.4% vs. LOSD: 60.5%, $p = 0.35$), tremor (LOTS: 32.5% vs. LOSD: 16.3%, $p = 0.33$), and speech difficulties (LOTS: 65.9% vs. LOSD: 51.2%, $p = 0.70$) were not statistically different. Dystonia was reported in 9 cases (4 LOTS [one potentially tardive dystonia/dyskinesia], 5 LOSD), with 2 cases of athetotic/dyskinetic movements and dystonic speech.[23] Parkinsonism was rare, reported in 1 LOTS[24] and 1 LOSD patient.[25]

Significant correlations between clinical characteristics included: swallowing problems with UMN features ($r = 0.26$, $p = 0.0007$); tremor with ataxia ($r = 0.21$, $p = 0.0067$); ataxia with cognitive symptoms ($r = 0.29$, $p = 0.0001$), speech problems ($r = 0.43$, $p < 0.0001$) and UMN features ($r = 0.16$, $p = 0.034$); and psychosis/bipolar symptoms with cognitive symptoms ($r = 0.29$, $p = 0.0001$) and speech problems ($r = 0.16$, $p = 0.038$). Age of onset correlated positively with LMN features ($r = 0.17$, $p = 0.033$) and negatively with ataxia ($r = -0.22$, $p = 0.0064$), cognitive symptoms ($r = -0.20$, $p = 0.013$), psychosis/bipolar symptoms ($r = -0.22$, $p = 0.0074$), and speech problems ($r = -0.25$, $p = 0.0018$). Age at presentation ($n = 149$, $r = 0.49$, $p < 0.0001$) and age at scan ($n = 112$, $r = 0.38$, $p < 0.0001$) correlated with disease duration.

Clinical comparisons with age of symptom onset and disease duration

Comparing age of symptom onset as a dichotomous variable (younger age of onset: age < 18 years; older onset: ≥18 years), of 151 LOGG patients with data, 81 (53.6%) presented with a younger age of onset (Fig. 2B,C). In LOTS ($n = 111$) in younger versus older onset patients, differences in LMN features (75.4% vs. 89.1%) were not significant ($p = 0.55$). In LOSD ($n = 40$), psychosis/bipolar symptoms were only present in younger onset LOSD (25.0% vs. 0%); differences in cognitive symptoms (56.3% vs. 20.8%) were not significant ($p = 0.17$). Speech disturbances were similar in LOTS but commoner in younger onset LOSD (81.3% vs. 29.2%, Fisher's $p = 0.025$).

We were mindful of potential biases introduced by different disease duration in the younger versus older symptom onset groups, as patients with younger onset symptoms may have longer disease duration or may have been evaluated earlier in their course. Disease duration was therefore assessed as a dichotomous variable (shorter duration: ≤10 years [$n = 40$]; longer duration: >10 years [$n = 111$]). Reported ataxia in those with available disease duration ($n = 151$) with shorter versus longer duration LOGG (57.5% vs. 77.5%, $p = 0.12$), was mainly driven by LOTS and not significant.

Comparison between major LOGG phenotypes

We assessed major LOGG clinical phenotypes: ataxia versus neuromuscular (no ataxia), psychosis/bipolar symptoms versus no psychosis/bipolar symptoms, and cognitive symptoms versus no cognitive symptoms, irrespective of age at disease onset or disease duration, in relation to other clinical symptoms (Fig. 3).

Clinical differences between ataxia (cerebellar) versus non-ataxia (neuromuscular) subgroups

LOGG with ataxia ($n = 120$) versus non-ataxic patients, had more frequently reported speech disturbance (75.0% vs. 28.3%, $p < 0.0001$), cognitive symptoms (51.0% vs. 19.6%, $p = 0.0014$), and tremor (34.2% vs. 13.0%, $p = 0.048$). In LOTS with ataxia ($n = 94$) versus non-ataxic, there were similar observations in speech ($p < 0.0001$) and tremor ($p = 0.022$) (driving differences

Table 1. Summary of included papers in LOGG systematic review, highlighting clinical symptoms, and imaging features.

	Disease subtype			Demographic details					Clinical features								Imaging features				
Paper first author, publication year*	LOGG, n	LOTS, n	LOSD, n	M: F	Ethnicity (AJ: other)	Age onset, yr range	Age pres, yr range	Age scan, yr range	LMN, n (% case series)	UMN, n (% case series)	Ataxia, n (% case series)	Cognit, n (% case series)	Psych, n (% case series)	Speech, n (% case series)	Swallow, n (% case series)	Tremor, n (% case series)	MR, n	CT, n	Cerebellar atrophy, n (% case series)	Cerebral atrophy, n (% case series)	Brainstem Atrophy, n (% case series)
Oonk, 1979	2	2	0	0:2	NR	20	34–37	34–37	2 (100)	2 (100)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	1 (50)	0	2	0 (0)	0 (0)	0 (0)
Willner, 1981	3	3	0	1:2	3:0	4–12	26–37	26–37	3 (100)	3 (100)	3 (100)	2 (67)	1 (33)	3 (100)	0 (0)	0 (0)	0	3	3 (100)	2 (67)	0 (0)
Argov, 1984	1	1	0	1:0	1:0	Late teens	33	33	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	0	1	0 (0)	0 (0)	0 (0)
Mitsumoto, 1985	3	3	0	3:0	1:2	Childhood-college	30–36	30–36	3 (100)	2 (67)	2 (67)	2 (67)	0 (0)	2 (67)	0 (0)	NR	2	1	3 (100)	0 (0)	0 (0)
Parnes, 1985	1	1	0	1:0	0:1	5	34	34	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	NR	NR	NR	0	1	0 (0)	1 (100)	0 (0)
Oates, 1986	1	1	0	1:0	0:1	8	24	24	1 (100)	0 (0)	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	0	1	1 (100)	0 (0)	0 (0)
Karni, 1988	1	1	0	0:1	1:0	37	39	39	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0	1	1 (100)	0 (0)	0 (0)
Lichtenberg, 1988	1	1	0	0:1	1:0	Childhood	27	27	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0	1	0 (0)	0 (0)	0 (0)
Streifler, 1989	3	3	0	0:3	3:0	Secondary school-42	24–44	23–43	3 (100)	2 (67)	3 (100)	1 (33)	3 (100)	3 (100)	0 (0)	NR	0	3	3 (100)	0 (0)	0 (0)
Mitsuo, 1990	1	0	1	1:0	0:1	10	35	35	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	1	1	1 (100)	0 (0)	0 (0)
Praamstra, 1990	1	1	0	1:0	NR	5	17	24	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0	1	1 (100)	1 (100)	0 (0)
Barnes, 1991	1	1	0	1:0	0:1	Adolescent	42	42	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	1	0	1 (100)	0 (0)	1 (100)
Federico, 1991	2	0	2	2:0	0:2	25–30	43–49	43–49	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)	NR	NR	2 (100)	0	2	NR	NR	NR
Renshaw, 1992	1	1	0	1:0	1:0	14	35	36	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)	NR	NR	NR	1	0	1 (100)	0 (0)	0 (0)
Hurowitz, 1993	1	1	0	0:1	0:1	20	37	37	0 (0)	1 (100)	0 (0)	1 (100)	0 (0)	NR	NR	NR	0	1	0 (0)	0 (0)	0 (0)
Streifler, 1993	10	10	0	4:6	10:0	5–41	19–51	19–51	10 (100)	1 (10)	9 (90)	7 (70)	6 (60)	6 (60)	0 (0)	0 (0)	9	10	10 (100)	0 (0)	0 (0)
Inzelberg, 1994	1	1	0	1:0	1:0	Mid-teens	38	40	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)	1	0	1 (100)	0 (0)	0 (0)
Schnorf, 1995	1	0	1	1:0	0:1	20	59	51	1 (100)	1 (100)	1 (100)	0 (0)	NR	NR	NR	1 (100)	1	0	1 (100)	0 (0)	0 (0)
De Gasperi, 1996	1	1	0	0:1	1:0	Adolescent	32	31	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	1 (100)	1	0	1 (100)	0 (0)	0 (0)
Redonnet-Vernhet, 1996	1	0	1	1:0	0:1	NR	17	17	1 (100)	NR	1 (100)	NR	NR	NR	NR	NR	1	0	1 (100)	0 (0)	0 (0)
Harding, 1997	2	2	0	1:1	2:0	30–35	45–50	45–50	2 (100)	1 (50)	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0	2	2 (100)	0 (0)	2 (100)
Hund, 1997	4	4	0	2:2	0:4	12–17	26–39	26–39	4 (100)	3 (75)	4 (100)	0 (0)	0 (0)	4 (100)	0 (0)	4 (100)	4	0	4 (100)	0 (0)	0 (0)
Manor, 1997	1	1	0	0:1	1:0	NR	26	26	NR	NR	1 (100)	NR	1 (100)	1 (100)	0 (0)	NR	0	1	1 (100)	0 (0)	0 (0)
Hamner, 1998	1	1	0	1:0	1:0	20	45	45			1 (100)	1 (100)		1 (100)	0 (0)	1 (100)	1	1	1 (100)	0 (0)	0 (0)

(Continued)

Table 1 Continued.

Paper first author, publication year*	Disease subtype: LOGG, *n*	LOTS, *n*	LOSD, *n*	Demographic details: M: F	Ethnicity (AJ: other)	Age onset, yr range	Age pres, yr range	Age scan, yr range	Clinical features: LMN, *n* (% case series)	UMN, *n* (% case series)	Ataxia, *n* (% case series)	Cognit, *n* (% case series)	Psych, *n* (% case series)	Speech, *n* (% case series)	Swallow, *n* (% case series)	Tremor, *n* (% case series)	Imaging features: MR, *n*	CT, *n*	Cerebellar atrophy, *n* (% case series)	Cerebral atrophy, *n* (% case series)	Brainstem Atrophy, *n* (% case series)
									1 (100)	1 (100)			1 (100)								
Hara, 1998	1	0	1	1:0	0:1	26	31	31	0 (0)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	1	1	1 (100)	0 (0)	0 (0)
Förster, 1999	1	1	0	1:0	NR	17	32	32	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	1 (100)	1	1	1 (100)	0 (0)	0 (0)
Gomez-Brouchet, 1999	1	0	1	1:0	NR	Adolescent	46	46	1 (100)	NR	0 (0)	NR	1 (100)	1 (100)	0 (0)	NR	1	0	0 (0)	0 (0)	0 (0)
Salman, 2001	3	0	3	1:2	0:3	3–11	27–29	27–29	3 (100)	3 (100)	3 (100)	3 (100)	0 (0)	3 (100)	0 (0)	2 (67)	3	0	3 (100)	1 (33)	0 (0)
Yoshizawa, 2002	1	0	1	1:0	0:1	15	35	35	1 (100)	1 (100)	0 (0)	0 (0)	NR	NR	NR	NR	1	0	0 (0)	0 (0)	0 (0)
Inglese, 2003	9	9	0	6:3	6:3	12–36	20–58	20–58	9 (100)	0 (0)	NR	0 (0)	4 (44)	8 (89)	0 (0)	9 (100)	9	0	9 (100)	0 (0)	0 (0)
Rucker, 2004	14	14	0	8:6	7:7	8–20s	24–53	24–53	8 (57)	3 (21)	11 (79)	0 (0)	3 (21)	8 (57)	0 (0)	9 (64)	14	0	13 (93)	3 (21)	5 (36)
Frey, 2005	3	3	0	0:3	2:1	8–18	25–46	25–46	3 (100)	3 (100)	3 (100)	3 (100)	2 (67)	2 (67)	0 (0)	1 (33)	0	3	2 (67)	0 (0)	0 (0)
Takado, 2007	1	0	1	1:0	0:1	42	46	46	1 (100)	1 (100)	NR	NR	NR	NR	NR	NR	1	0	1 (100)	0 (0)	0 (0)
Elstein, 2008	8	8	0	4:2	6:0		28–44	28–44	6 (100)	0 (0)	5 (83)	6 (100)	4 (67)	3 (50)	0 (0)	1 (17)	6	0	5 (83)	0 (0)	0 (0)
Peters, 2008	1	1	0	1:0	0:1	18	23	23	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1	0	1 (100)	0 (0)	0 (0)
Godeiro-Junior, 2009	1	1	0	1:0	0:1	22	30	30	1 (100)	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	1	0	0 (0)	0 (0)	1 (100)
Maegawa, 2009	3	1	2	2:1	NR	Adolescent-12	16–20	16–20	2 (67)	1 (33)	3 (100)	2 (67)	3 (100)	2 (67)	1 (33)	1 (33)	3	0	3 (100)	0 (0)	0 (0)
Tallaksen, 2009	1	0	1	1:0	0:1	2	19	18	0 (0)	NR	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	1	0	1 (100)	0 (0)	0 (0)
Ahn, 2010	1	0	1	0:1	0:1	NR	23	23	1 (100)	NR	NR	NR	NR	1 (100)	1 (100)	0 (0)	1	0	0 (0)	0 (0)	0 (0)
Delnooz, 2010	6	0	6	3:3	0:6	18–47	26–62	26–62	6 (100)	2 (33)	3 (50)	NR	NR	2 (33)	2 (33)	0 (0)	6	0	6 (100)	0 (0)	0 (0)
Gagoski, 2010	4	4	0	3:1	NR	NR	38–45	38–45	NR	NR	NR	NR	NR	NR	NR	NR	4	0	4 (100)	0 (0)	0 (0)
Masciullo, 2010	1	0	1	1:0	0:1	45	54	54	1 (100)	0 (0)	0 (0)	1 (100)	NR	1 (100)	0 (0)	NR	1	0	1 (100)	0 (0)	0 (0)
Gort, 2012	1	0	1	1:0	0:1	14	NR	NR	NR	NR	1 (100)	NR	NR	1 (100)	0 (0)	0 (0)	1	0	1 (100)	NR	NR
Tazen, 2012	1	0	1	0:1	0:1	18	30	30	0 (0)	0 (0)	1 (100)	NR	NR	1 (100)	0 (0)	NR	1	0	1 (100)	0 (0)	0 (0)
Jamrozik, 2013	1	1	0	1:0	0:1	30			1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1	0	1 (100)	0 (0)	0 (0)
Kang, 2013	1	0	1	0:1	NR	53	55	55	1 (100)	0 (0)	0 (0)	0 (0)	NR	0 (0)	0 (0)	0 (0)	1	0	0 (0)	0 (0)	0 (0)
Prihodova, 2013	2	2	0	0:2	0:2	10	17–29	17–29	2 (100)	0 (0)	2 (100)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	1	0	2 (100)	0 (0)	2 (100)
Rattay, 2013	1	0	1	0:1	0:1	44	46	48	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1	0	0 (0)	0 (0)	0 (0)
Yasui, 2013	1	0	1	0:1	0:1	6	20	20	1 (100)	NR	1 (100)	1 (100)	NR	NR	NR	0 (0)	1	0	1 (100)	0 (0)	0 (0)

(*Continued*)

Table 1 Continued.

Paper first author, publication year*	Disease subtype: LOGG, n	LOTS, n	LOSD, n	Demographic details: M:F	Ethnicity (AJ: other)	Age onset, yr range	Age pres, yr range	Age scan, yr range	Clinical features: LMN, n (% case series)	UMN, n (% case series)	Ataxia, n (% case series)	Cognit, n (% case series)	Psych, n (% case series)	Speech, n (% case series)	Swallow, n (% case series)	Tremor, n (% case series)	Imaging features: MR, n	CT, n	Cerebellar atrophy, n (% case series)	Cerebral atrophy, n (% case series)	Brainstem Atrophy, n (% case series)
Deik, 2014	1	1	0	0:1	1:0	20s	53	53	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	1	0	1 (100)	0 (0)	0 (0)
Chardon, 2015	1	0	1	1:0	0:1	50	54	54	1 (100)	0 (0)	0 (0)	0 (0)	NR	1 (100)	0 (0)	1 (100)	1	0	0 (0)	0 (0)	0 (0)
Grim, 2015	1	1	0	0:1	1:0	10	22	22	0 (0)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	1	0	1 (100)	0 (0)	0 (0)
Pretegiani, 2015	1	0	1	1:0	0:1	NR	74	74	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)	1	0	0 (0)	0 (0)	0 (0)
Scarpelli, 2015	1	1	0	1:0	0:1	28	53	53	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NR	1	0	1 (100)	0 (0)	0 (0)
Stendel, 2015	2	2	0	1:1	0:2	16–17	23–30	16–19	1 (50)	1 (50)	2 (100)	0 (0)	2 (100)	2 (100)	0 (0)	0 (0)	2	0	0 (0)	0 (0)	0 (0)
Liguori, 2016	1	1	0	0:1	1:0	9	30	30	0 (0)	0 (0)	1 (100)	0 (0)	1 (100)	1 (100)	1 (100)	0 (0)	1	0	1 (100)	0 (0)	0 (0)
Steiner, 2016	1	1	0	1:0	NR	Early childhood	47	47	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1	0	1 (100)	0 (0)	0 (0)
Barritt, 2017	1	1	0	1:0	0:1	14	35	35	1 (100)	1 (100)	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	1 (100)	1	0	1 (100)	0 (0)	0 (0)
Maier, 2017	1	1	0	1:0	0:1	17	32	32	1 (100)	1 (100)	1 (100)	0 (0)	0 (0)	1 (100)	1 (100)	1 (100)	1	0	1 (100)	0 (0)	0 (0)
Sung, 2018	1	0	1	0:1	0:1	37	40	40	1 (100)	0 (0)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)		1	0	1 (100)	1 (100)	0 (0)
Gahramanova, 2019	1	1	0	0:1	NR	NR	20	20	NR	NR	NR	NR	NR	NR	NR	0 (0)	1	0	0 (0)	0 (0)	0 (0)
Jahnova, 2019	14	14	0	5:9	0:14	10–33	18–54		12 (86)	0 (0)	12 (86)	4 (29)	5 (36)	10 (71)	0 (0)	9 (64)	14	0	14 (100)	0 (0)	0 (0)
Khoueiry, 2020	2	0	2	1:0	NR	47–49	55–57	55–57	2 (100)	0 (0)	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2	0	0 (0)	0 (0)	0 (0)
Stephen, 2020	10	7	3	6:4	NR	8–36	21–62	21–62	10 (100)	0 (0)	10 (100)	1 (10)	0 (0)	6 (60)	0 (0)	3 (30)	10	7	7 (70)	1 (10)	2 (20)
Masingue, 2020	12	4	8	3:9	0:12	10–26	28–51	28–51	12 (100)	9 (75)	7 (58)	8 (67)	4 (33)	6 (50)	6 (50)	NR	12	0	11 (92)	5 (42)	0 (0)
Alonso-Pérez, 2021	2	0	2	1:1	0:2	Adolescent	41–46	41–46	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	0 (0)	2	0	0 (0)	0 (0)	0 (0)
Hölzer, 2021	1	1	0	1:0	0:1	13	18	18	1 (100)	1 (100)	1 (100)	1 (100)	0 (0)	1 (100)	0 (0)	1 (100)	1	0	1 (100)	0 (0)	0 (0)
Májovská, 2022	5	5	0	2:3	0:5	6–20	29–45	28–41	5 (100)	NR	5 (100)	1 (20)	2 (40)	5 (100)	0 (0)	4 (80)	5	0	5 (100)	1 (20)	5 (100)

Abbreviations: age pres, age at presentation; age onset, age at symptom onset; AJ, Ashkenazi–Jewish; cognit, cognitive symptoms/signs; LMN, lower motor neuron clinical signs; LOGG, late-onset GM2 gangliosidosis; LOTS, Late-onset Tay-Sachs disease; LOSD, Late-onset Sandhoff disease; M:F, male:female; MR, MRI; NR, not recorded; Psych, psychosis/bipolar symptoms; speech, speech disturbance; swallow, swallowing symptoms/dysfunction; UMN, upper motor neuron clinical signs; yr, years.

*Full details of the included references are shown in Supplementary Data S1. Genotypes (where available) are shown in Supplementary Table S1.

Table 2. Demographic details, clinical details, and brain imaging modality of the LOGG cohort.

Parameter	Subject group			
	Total LOGG (n = 170)	LOTS (n = 127)	LOSD (n = 43)	LOTS vs. LOSD p-value
Demographic details				
Male:Female (% female)	88:82 (48.2)	63:64 (50.4)	25:18 (41.9)	0.33
Age at onset, yr ± SD	19.5 ± 10.5	17.9 ± 8.2	23.9 ± 14.4	**0.017**
Missing, n (%)	19 (11.2)	16 (12.6)	3 (7.0)	
Age at assessment, yr ± SD	36.6 ± 11.2	35.4 ± 9.9	40.1 ± 13.9	0.051
Missing, n (%)	6 (3.5)	5 (3.9)	1 (2.3)	
Age at scan, yr ± SD	36.4 ± 11.4	35.0 ± 10.0	39.9 ± 13.9	0.060
Missing, n (%)	47 (28.6)	39 (32.5)	7 (17.1)	
Ethnicity/Ancestry				**<0.0001**
Ashkenazi-Jewish, n (%)	50 (29.4)	50 (39.3)	0 (0)	
Other non-Jewish European, n (%)	71 (41.8)	53 (41.7)	18 (41.9)	
French Canadian, n (%)	4 (2.4)	3 (2.4)	1 (2.3)	
South Asian, n (%)	2 (1.2)	1 (0.8)	1 (2.3)	
East Asian, n (%)	6 (3.5)	0 (0)	6 (14.0)	
African, n (%)	3 (1.8)	0 (0)	3 (7.0)	
Middle Eastern, n (%)	1 (0.6)	0 (0)	1 (2.3)	
Missing, n (%)	33 (19.4)	20 (15.7)	13 (30.2)	
Clinical features				
Lower motor neuron, n (%)	136 (81.9)	99 (80.5)	37 (86.1)	0.41
Upper motor neuron, n (%)	57 (34.3)	42 (34.2)	15 (43.9)	0.93
Ataxia, n (%)	120 (72.3)	94 (76.4)	26 (60.5)	**0.044**
Tremor, n (%)	47 (28.3)	40 (32.5)	7 (16.3)	**0.042**
Cognitive symptoms, n (%)	71 (42.8)	56 (45.5)	15 (34.9)	0.22
Psychiatric symptoms (Psychosis/bipolar), n (%)	47 (28.3)	43 (35.0)	4 (9.3)	**0.0014**
Speech symptoms, n (%)	103 (62.1)	81 (65.9)	22 (51.2)	0.088
Swallowing problems, n (%)	13 (7.8)	5 (4.1)	8 (18.6)	**0.0051**
Missing, n (%)	4 (2.4)	4 (3.1)	0 (0)	
Brain imaging modality				
MRI, n (%)	144 (84.7)	104 (81.9)	40 (93.0)	
CT only, n (%)	26 (15.3)	23 (18.1)	3 (7.0)	
Both MRI and CT, n (%)	12 (7.1)	11 (8.7)	1 (2.3)	
Description of severity of cerebellar atrophy, n missing (%)	58 (34.1)	50 (39.4)	8 (18.6)	

All values and % are based on non-missing data save ethnicity/ancestry, where the missing category is included to give a more accurate representation of ethnicity/ancestry breakdown. Significant p-values are highlighted in bold

Clinical findings were classified as: UMN involvement (spasticity, hyperreflexia, etc.), LMN involvement (atrophy, fasciculations, hyporeflexia, etc.), cerebellar ataxia, cognitive deficits/dementia (patient/clinician reported), psychiatric symptoms (specifically psychosis or bipolar affective disorders symptoms), speech difficulties (dysarthria, stuttering, etc.), swallowing difficulties, tremor, and other movement disorders (parkinsonism, etc.).

Abbreviations: aLOGG, late-onset GM2 gangliosidosis; LOSD, late-onset Sandhoff disease; LOTS, late-onset Tay-Sachs disease; SD, standard deviation; yr, years.

in LOGG), and more frequent LMN signs (87.2% vs. 58.6%, p = 0.0049). In comparison, LOSD with ataxia (n = 26) only had greater reported cognitive symptoms (53.9% vs. 5.9%, p = 0.0084). Tremor was infrequently reported in LOSD, regardless of ataxia presentation.

Clinical differences between neuropsychological phenotype subgroups

LOGG with reported psychosis/bipolar symptoms (n = 47) versus those without, had more frequent concurrent cognitive symptoms/signs (66.0% vs. 33.6%, p = 0.0007). This observation was similar in (and likely driven by) LOTS (n = 43, 67.4% vs. 33.8%, p = 0.0021), while LOSD had no significant associations.

LOGG with reported cognitive symptoms (n = 71) were more likely to have psychosis/bipolar symptoms (43.7% vs. 16.8%, p = 0.0007) and ataxia (87.3% vs. 61.1%, p = 0.0014). LOTS with cognitive symptoms (n = 56), had more frequent psychosis/bipolar symptoms (52.8% vs. 20.9%, p = 0.0021), and LMN features (94.6% vs. 68.7%, p = 0.0014). In LOSD, those with cognitive symptoms (n = 15) had more frequent ataxia (93.3% vs. 42.9%, p = 0.0084).

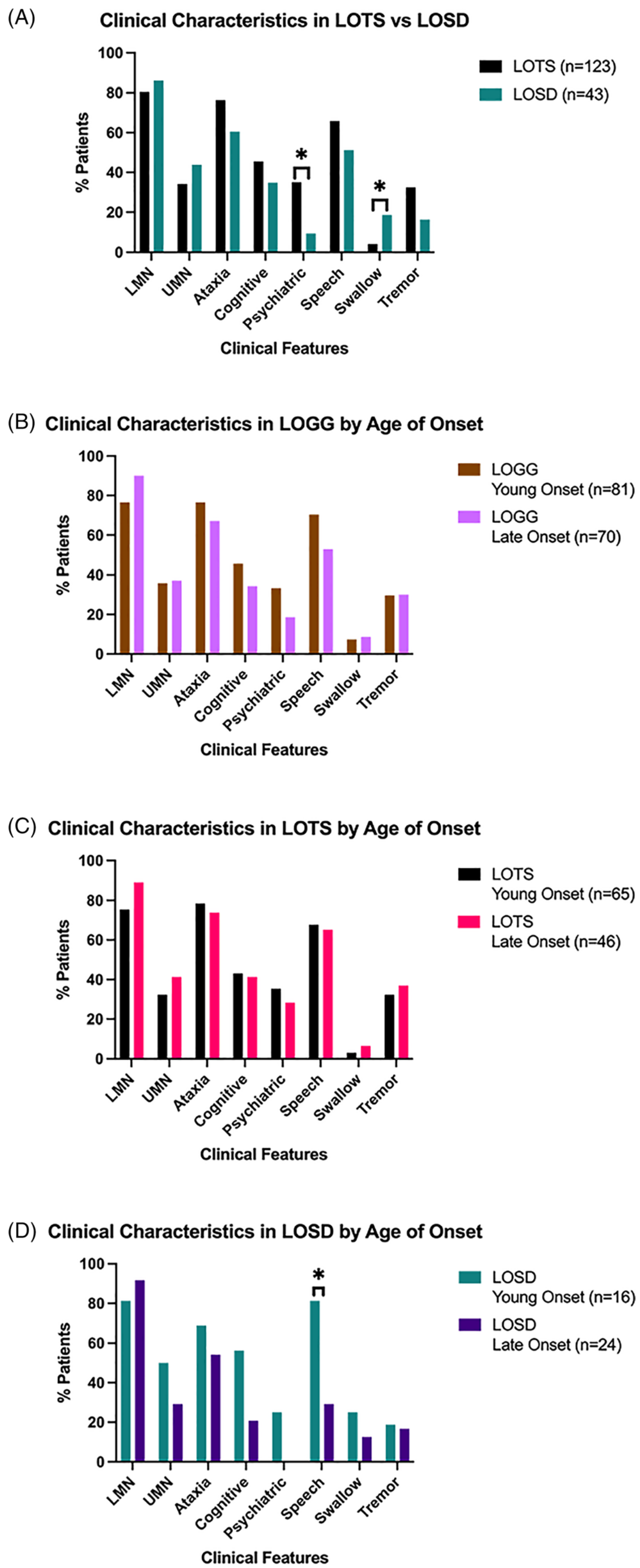

Figure 2. Clinical characteristics of LOGG, LOTS, and LOSD and by age of onset subgroups. Bar graphs illustrate differences in clinical characteristics comparing LOTS to LOSD (2A); with comparison in young (<18 years) and late (≥18 years) onset subgroups in LOGG (2B), LOTS (2C), and LOSD (2D). Significance label * indicates $p < 0.05$. LMN: lower motor neuron clinical signs; UMN: upper motor neuron clinical signs; cognitive: cognitive symptoms/signs; psychiatric: psychosis/bipolar symptoms; speech: speech disturbance; swallow: swallowing symptoms/dysfunction.

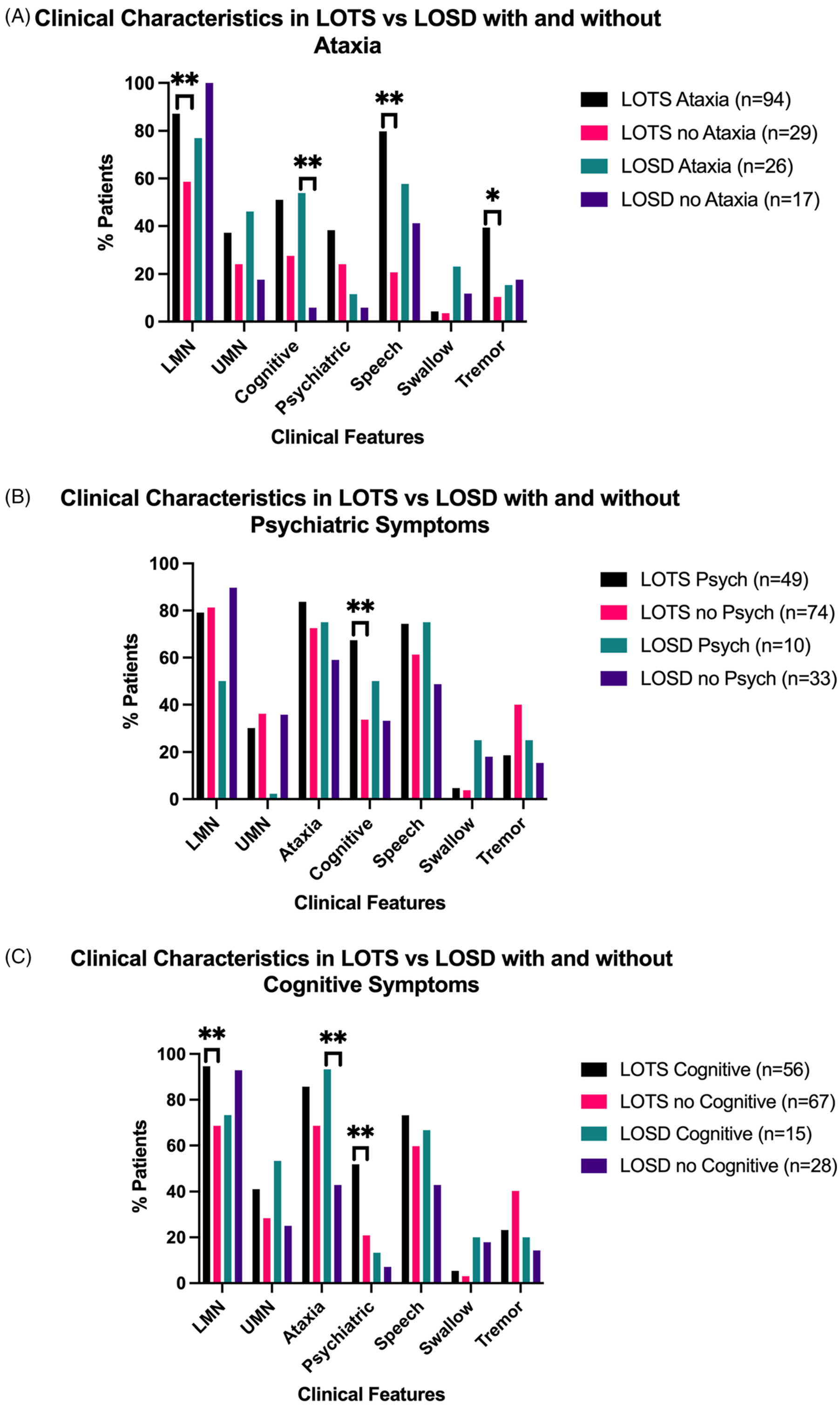

Figure 3. Clinical characteristics of LOTS, and LOSD by ataxia, psychiatric, and cognitive symptoms. Bar graphs illustrate differences in clinical characteristics comparing LOTS to LOSD in the main phenotypes: (A) ataxic versus non-ataxic (neuromuscular) phenotypes; (B) psychiatric versus nonpsychiatric phenotype; (C) cognitive disorder versus normal cognition phenotypes. Significance labels: * indicates $p < 0.05$, ** $p < 0.01$. LMN: lower motor neuron clinical signs; UMN: upper motor neuron clinical signs; cognitive: cognitive symptoms/signs; psychiatric: psychosis/bipolar symptoms; speech: speech disturbance; swallow: swallowing symptoms/dysfunction.

Imaging features

Structural MRI brain imaging findings were available for 104 out of 127 LOTS and 40 out of 43 LOSD, with only CT head data available for the remainder. Cerebellar atrophy was common in LOGG (139 out of 170 [81.8%]) but more common in LOTS (LOTS: 89.0% vs. LOSD: 60.5%, $p < 0.0001$). Brainstem atrophy, reported only in LOTS, was described infrequently (18 out of 127 [14.2%], $p = 0.0074$) and when present, was almost exclusively (17 out of 18, 94.4%) concomitant with cerebellar atrophy. Cerebral atrophy was occasionally noted in LOGG (16 out of 170 [9.4%]) and similar in LOTS versus LOSD.

When a description of estimated severity of cerebellar atrophy (LOGG $n = 112$, including when normal imaging was explicitly stated) was available: 50.0% had severe cerebellar atrophy and 27.7% had normal cerebellar imaging. When comparing the individual diseases (LOTS: $n = 77$, LOSD: $n = 35$), severe cerebellar atrophy was more common in LOTS (LOTS: 61.0% vs. LOSD: 25.7%, $p = 0.0005$). When observing trends in severity of cerebellar atrophy, moderate atrophy was more common in LOTS (14.3%) versus LOSD (5.7%), whereas mild atrophy (LOTS: 6.5% vs. LOSD: 20.0%) and no atrophy (LOTS: 18.2% vs. LOSD: 48.6%), were more common in LOSD (Mantel–Haenszel χ^2 $p < 0.0001$).

The pattern of cerebellar atrophy was described in 30 LOTS and 5 LOSD, generally describing global cerebellar atrophy (21 out of 30 LOTS, 2 out of 5 LOSD); other descriptions included vermian-predominant atrophy (5 out of 28 LOTS and 3 out of 5 LOSD). Thinning of the corpus callosum was reported only in LOTS (12 out of 127, 9.4%). One report of cervical spine MRI imaging in LOSD revealed dorsal column degeneration and generalized cord atrophy.[26]

Imaging group-wise comparisons

We assessed the major LOGG clinical phenotypes by comparing imaging findings between the major clinical phenotypes (as above) with concurrent imaging findings, irrespective of age at disease onset or disease duration (Fig. 4).

Imaging in ataxic versus non-ataxic (neuromuscular) subgroups

LOGG with reported ataxia ($n = 120$) had more frequent cerebellar atrophy (87.5% vs. 65.2%, $p = 0.007$). In LOGG with ataxia and description of cerebellar atrophy severity ($n = 112$, missing = 58), ataxic LOGG had higher rates of reported severe (57.9% vs. 33.3%) and moderate atrophy (14.5% vs. 5.6%) and lower rates of mild (7.9% vs. 16.7%) and no atrophy (19.7% vs. 44.4%), Mantel–Haenszel χ^2 $p = 0.012$. In LOTS, there were similar rates of cerebellar atrophy in those with and without ataxia, whereas ataxic LOSD had more frequent cerebellar atrophy (ataxic: 76.9% vs. non-ataxic: 35.3%, $p = 0.043$) (Fig. 4A). When cerebellar atrophy severity was reported, in LOTS ($n = 77$), both ataxic/non-ataxic patients had similar reported rates of severe cerebellar atrophy (ataxic: 60.3% vs. non-ataxic: 63.2%). In comparison, in LOSD ($n = 35$), severe and moderate atrophy were described only in ataxic patients (50% and 11.1%, respectively), while mild (ataxic: 5.6% vs. non-ataxic: 35.5%) and no atrophy (ataxic: 33.3% vs. non-ataxic: 64.7%), were more common in those without ataxia, Mantel–Haenszel χ^2 $p = 0.0063$. In LOTS, apparent differences in cerebral atrophy (non-ataxic: 20.7% vs. ataxic: 7.5%, $p = 0.26$) were nonsignificant. In LOSD, only patients with ataxia had cerebral atrophy but was nonsignificant (11.5% vs. 0%, $p = 0.88$).

Imaging in cognitive/neuropsychiatric phenotype subgroups

Brainstem atrophy was less common in LOTS with psychosis/bipolar symptoms (4.7%) versus those without (20.0%), $p = 0.030$, without other associations (Fig. 4B, C).

Comparison of clinical characteristics between cerebellar atrophy subgroups

In LOGG with cerebellar atrophy ($n = 135$) versus without, there were higher rates of ataxia (77.8% vs. 48.4%, $p = 0.0080$). In LOSD with cerebellar atrophy, UMN features (53.9% vs. 5.9%, $p = 0.0096$) and ataxia (76.9% vs. 35.3%, $p = 0.050$) were more common (Fig. 4D). Of two patients with parkinsonism, the LOTS patient had severe cerebellar atrophy,[24] the LOSD patient (who had concomitant oculopalatal tremor) had normal imaging.[25]

Comparison of imaging findings by age of onset and disease duration

Age of onset correlated with reported cerebellar atrophy ($r = -0.21$, $p = 0.011$) and the severity of cerebellar atrophy ($r = -0.27$, $p = 0.0056$). There were no significant differences in cerebellar, cerebral, or brainstem atrophy in LOGG patients assessing dichotomous <18 versus ≥18 years age of onset, or within LOTS/LOSD.

Disease duration weakly correlated with cerebellar atrophy severity in LOGG ($r = 0.20$, $p = 0.048$), driven by LOTS ($r = 0.29$, $p = 0.015$) but not LOSD. In LOGG with disease duration data (duration ≤10 years [$n = 40$];

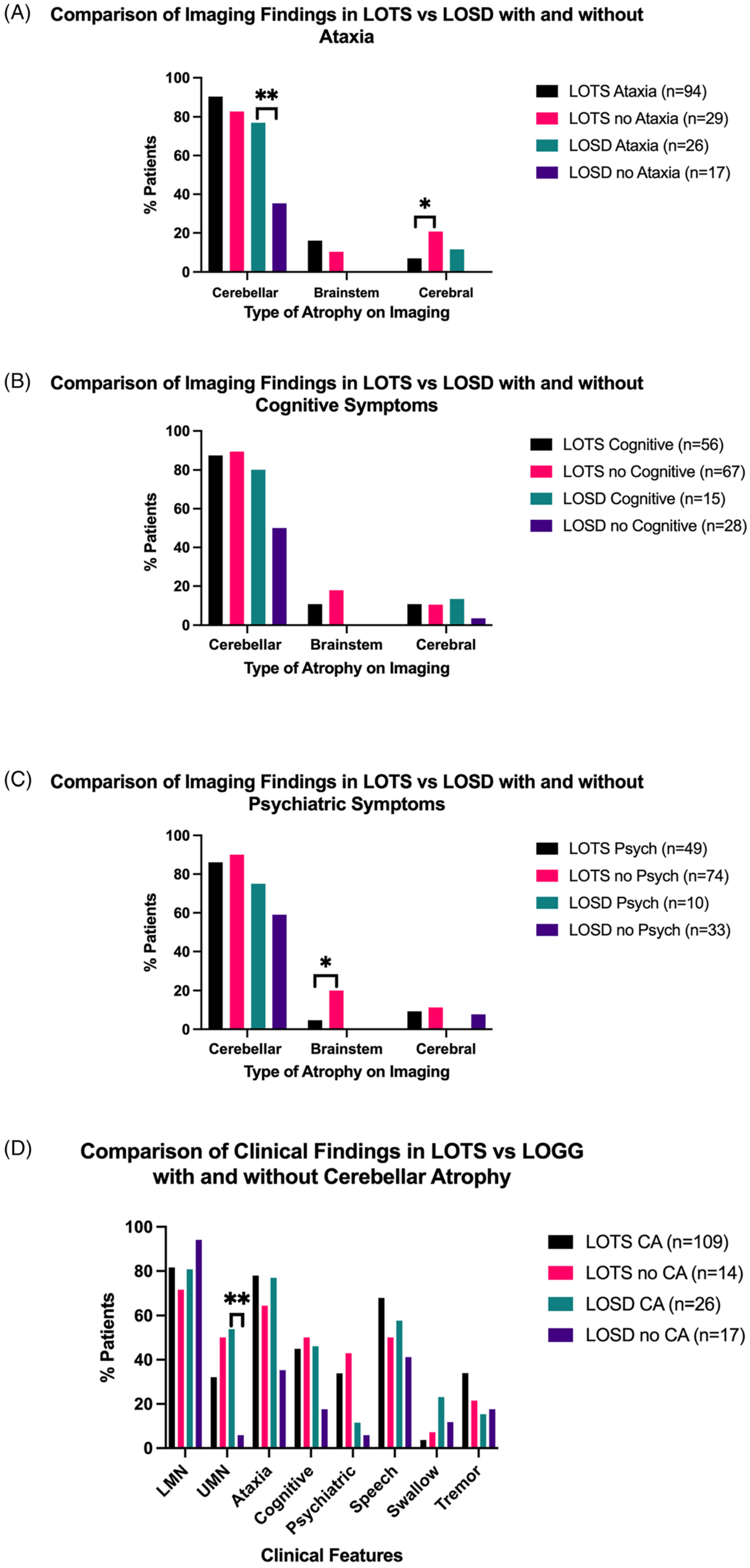
(A)
Comparison of Imaging Findings in LOTS vs LOSD with and without Ataxia
LOTS Ataxia (n=94)
LOTS no Ataxia (n=29)
LOSD Ataxia (n=26)
LOSD no Ataxia (n=17)
% Patients
Cerebellar
Brainstem
Cerebral
Type of Atrophy on Imaging
(B)
Comparison of Imaging Findings in LOTS vs LOSD with and without Cognitive Symptoms
LOTS Cognitive (n=56)
LOTS no Cognitive (n=67)
LOSD Cognitive (n=15)
LOSD no Cognitive (n=28)
% Patients
Cerebellar
Brainstem
Cerebral
Type of Atrophy on Imaging
(C)
Comparison of Imaging Findings in LOTS vs LOSD with and without Psychiatric Symptoms
LOTS Psych (n=49)
LOTS no Psych (n=74)
LOSD Psych (n=10)
LOSD no Psych (n=33)
% Patients
Cerebellar
Brainstem
Cerebral
Type of Atrophy on Imaging
(D)
Comparison of Clinical Findings in LOTS vs LOGG with and without Cerebellar Atrophy
LOTS CA (n=109)
LOTS no CA (n=14)
LOSD CA (n=26)
LOSD no CA (n=17)
% Patients
LMN
UMN
Ataxia
Cognitive
Psychiatric
Speech
Swallow
Tremor
Clinical Features

Figure 4. Imaging findings in LOTS and LOSD by main clinical phenotypes and clinical differences in the setting of cerebellar atrophy. Bar graphs highlight differences in imaging findings, including the presence of cerebellar, brainstem and cerebral atrophy across the main phenotypes: (A) ataxic versus non-ataxic (neuromuscular) phenotypes; (B) psychiatric versus nonpsychiatric phenotype; (C) cognitive disorder versus normal cognition phenotypes. (D) illustrates differences in clinical characteristics in LOTS/LOSD subgroups with either the presence or absence of a description of cerebellar atrophy on imaging. Significance labels: * indicates $p < 0.05$, ** $p < 0.01$. LMN: lower motor neuron clinical signs; UMN: upper motor neuron clinical signs; cognitive: cognitive symptoms/signs; psychiatric: psychosis/bipolar symptoms; speech: speech disturbance; swallow: swallowing symptoms/dysfunction; CA: cerebellar atrophy; psych: psychiatric phenotype.

duration >10 years [$n = 111$]; missing $n = 19$), at the latest scan description, rates of cerebellar atrophy were similar and also between LOTS and LOSD. In LOGG with cerebellar atrophy severity and disease duration data ($n = 104$, missing $n = 66$), patients with longer disease duration were more likely to have severe cerebellar atrophy (59.7% vs. 29.6%) and less likely to have mild (5.2% vs. 29.6%), or no cerebellar atrophy (23.4% vs. 29.6%), Mantel–Haenszel χ^2 $p = 0.0019$. Disease duration was not associated with brainstem or cerebral atrophy.

Clinical and imaging predictors of LOTS versus LOSD

Logistic regression analysis was used to determine predictors of LOTS versus LOSD. We initially performed a univariate screen of the 8 clinical features, age of onset, and 3 radiological features (cerebellar, brainstem, or cerebral atrophy, as other features were too infrequently reported). On this initial screen, of the 8 clinical features ($n = 166$), significant predictors with odds ratios (OR [95% confidence interval]) for LOTS relative to LOSD were the presence of swallowing symptoms, which was predictive of LOSD (OR 0.19 [0.057–0.60], $p = 0.0051$), whereas predictors of LOTS were psychosis/bipolar symptoms (OR 5.24 [1.95–18.32], tremor (OR 2.48 [1.02–6.06], $p = 0.046$), and ataxia (OR 2.12 [1.01–4.44], $p = 0.047$). For age of onset ($n = 151$, owing to missing values), a yearly increase was associated with a lower probability of LOTS (OR 0.95 [0.92–0.98], $p = 0.0032$). Radiological features were available in all patients ($n = 170$) and reported cerebellar atrophy (OR 5.23 [2.31–12.05], $p < 0.0001$), and, when available ($n = 112$), greater severity of cerebellar atrophy, used as an ordinal variable (OR 1.95 [1.40–2.71], $p < 0.0001$) were associated with LOTS. Although brainstem atrophy was only present in LOTS, its rarity did not reach significance ($p = 0.97$). We then included these 6 significant univariate predictors as simultaneous predictors, adjusted for each other, in a multivariate logistic regression model predicting LOTS, which was subjected to a backward elimination process. This resulted in a final model ($p < 0.0001$ for the model as a whole), with the following additive predictors of LOTS versus LOSD (odds ratio [95% confidence interval]) including: the presence of psychosis/bipolar (4.95 [1.59–19.52], $p = 0.011$), lack of swallowing symptoms (0.16 [0.036–0.64], $p = 0.011$), and cerebellar atrophy on imaging (5.81 [2.10–17.08], $p = 0.0009$). A lower age of onset (0.96 [0.93–1.00], $p = 0.075$) was marginally significant, given its correlation with psychosis/bipolar symptoms, and similarly the presence of tremor (2.50 [0.94–7.43], $p = 0.078$) but were felt sufficiently relevant to include in the final model. Of note, all of these features were also significant in the initial model with all 6 features, before the elimination, except for age of onset and tremor, which were marginally significant in the initial and final models. Figure 5 shows the comparative ORs (6A), receiver operating characteristic (ROC) curve (6B) and predicted probabilities of LOTS depending on different ages of onset with and without the other predictors (6C/D). It should be noted that LOTS has a greater *severity* of cerebellar atrophy when present, and when cerebral severity is included in the model in place of cerebellar atrophy, the predictors were also significant.

Multimodal imaging

In a study of multivoxel proton MR spectroscopy (^{1}H-MRS) in 9 LOTS patients, there was decreased N-acetylaspartate (NAA) in the thalamus, while differences in creatine (Cr) and choline (Cho) levels did not reach significance.[27] In a LOTS case, MRS revealed low NAA/Cr ratio and increased myo-inositol (ml)/Cr ratio, compatible with cerebellar atrophy, while fluorodeoxyglucose positron emission tomography (FDG-PET) revealed decreased glucose metabolism in the cerebellum, bilateral temporal, and occipital lobes.[28] In a LOSD case with oculopalatal tremor, MRI was unremarkable, while MRS revealed low NAA/Cr and Cho/Cr ratios in the pons and cerebellar white matter.[25] In a further LOSD case, FDG-PET using I-123 IMP revealed hypoperfusion in the cerebellum, brainstem, right basal ganglia, and thalamus.[29] MRS findings[13] in the 10 LOGG patients described in our previous work[20] revealed evidence of significant cerebellar atrophy, predominantly driven by the LOTS patients. MRS revealed a lower NAA and higher mI in LOGG, predominantly driven by LOTS. NAA, mI, and greater

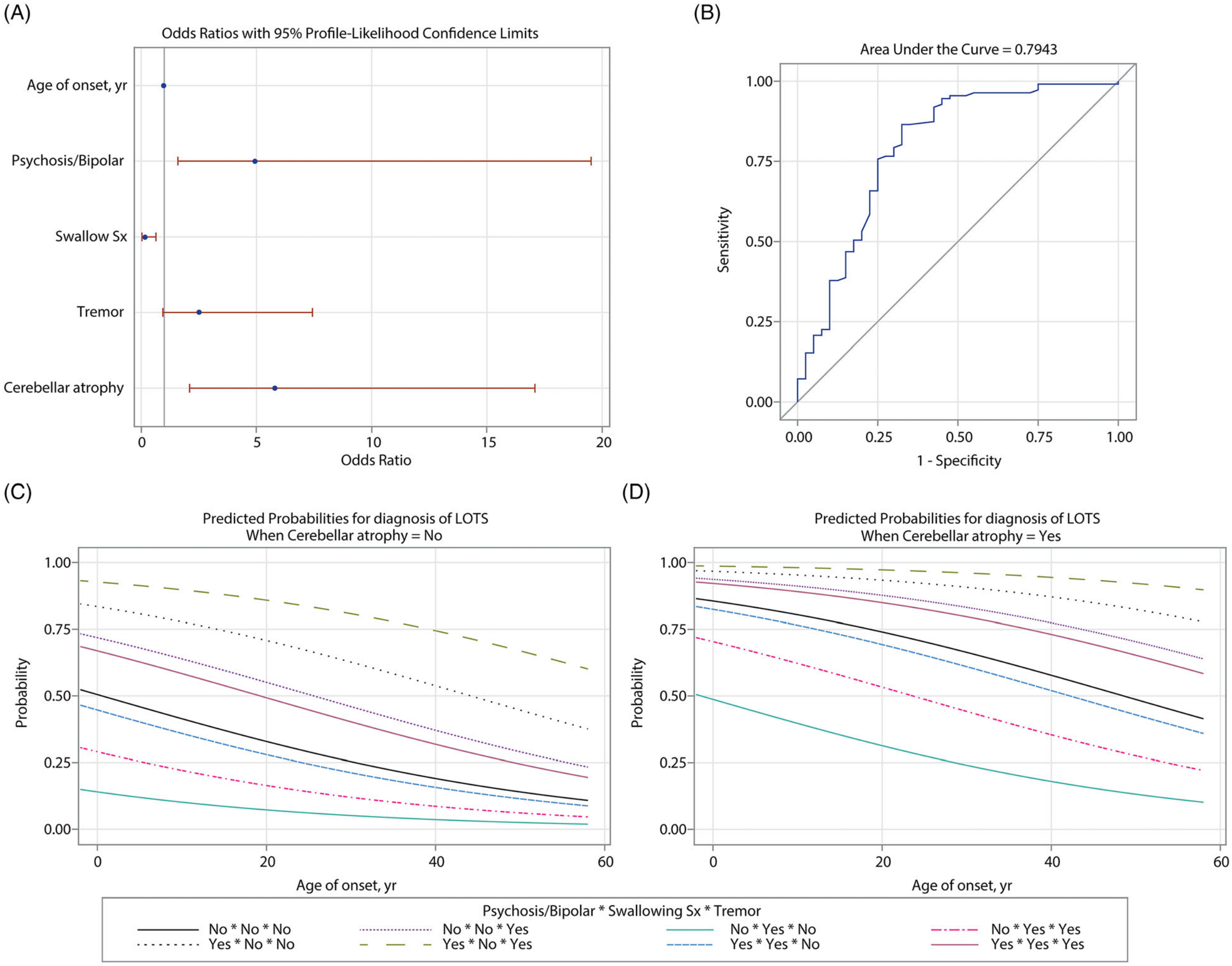

Figure 5. Clinical and imaging predictors of LOTS versus LOSD. This pertains to the final logistic regression model predicting LOTS versus LOSD: (A) the comparative odds ratios (OR) of LOTS relative to LOSD and 95% confidence intervals for the 5 predictors (age of onset in whole years, psychosis/bipolar symptoms, swallowing symptoms, tremor, and the presence of cerebellar atrophy on imaging); (B) the receiver operating characteristic (ROC) curve of the final model for prediction of a diagnosis of LOTS; (C) the relative predicted probabilities of LOTS depending on differing ages of onset with or without psychosis/bipolar symptoms, swallowing problems or tremor, in the absence of cerebellar atrophy on imaging, and (D) the presence of cerebellar atrophy on imaging. swallow Sx: swallowing symptoms/dysfunction; yr: years of age.

cerebellar volume loss correlated with higher ataxia severity assessed by clinical ataxia rating scales.[13]

Discussion

We performed a scoping review and analyzed the largest assembled cohort to date of reported LOGG patients with description of imaging findings. Using this large sample, we characterized the neuroimaging and clinical differences between LOTS and LOSD, and extended our hypothesis based on previous work[13,20] that there are both clinical and radiological differences between LOTS and LOSD, thus challenging previous conventions.[2,15] We assessed differences in clinical or imaging findings associated with age of symptom onset (controlling for disease duration). We compared both clinical and imaging findings between clinical phenotypes (ataxic/neuromuscular [non-ataxic], psychiatric, and cognitive) of LOTS, and LOSD separately. Lastly, we performed logistic regression analyses to identify clinical and imaging predictors of LOTS versus LOSD.

Given our large cohort, we first assessed general clinical characteristics. The most common clinical findings in LOGG patients were LMN features and ataxia. Higher rates of psychosis/bipolar symptoms in LOTS (consistent with the literature[2,12]) were a key differentiating feature on univariate testing, which, in the setting of a greater burden of cerebellar dysfunction in LOTS, may reflect the cerebellar cognitive affective syndrome.[19] Swallowing difficulties were infrequent but significantly more common in LOSD, consistent with the literature.[15] This may potentially be related to the higher prevalence of a neuromuscular phenotype with LMN involvement in LOSD.[30]

In comparing age of onset, younger onset LOGG patients may have more cerebellar (ataxia and speech disturbance) and cognitive/neuropsychiatric features. Differences were non-significant, except speech disturbances being more common in younger onset LOSD patients, highlighting a feature of more severe disease. It is noticeable that psychosis/bipolar was only present in young-onset LOSD, suggesting a poorly explained peculiarity of young-onset LOSD.

In comparing main LOGG clinical phenotypes, ataxic LOTS had higher rates of speech disturbance, cognitive symptoms and tremor, while ataxic LOSD tended to have only higher rates of cognitive symptoms, suggesting a difference in the motor versus non-motor ataxia symptoms between LOTS and LOSD.[31] LOTS patients with cognitive symptoms were more likely to have psychosis/bipolar symptoms (and vice versa), although this association was not present in LOSD. Interestingly, LOSD patients with cognitive symptoms were more likely to have ataxia but was not present in LOTS, highlighting a difference in the ataxic presentation between diseases.

When assessing imaging differences between LOTS and LOSD, the vast majority (~90%) of LOTS had reported cerebellar atrophy, whereas ~40% of LOSD had no cerebellar atrophy/normal imaging, supporting our previous observations.[20] Where there was a description of the degree of cerebellar atrophy, the cerebellar atrophy in LOTS tended to be more severe than LOSD. There were relatively few reports of the distribution of cerebellar atrophy, which was typically global, or was vermian greater than hemispheric, which is nonspecific compared to other cerebellar disorders. Brainstem atrophy was infrequently reported and only seen in LOTS, suggesting another disease-specific difference. This low prevalence, may be related to visually assessing scans, as opposed to detailed, quantitative measurements, particularly as Májovská et al. suggested that pontocerebellar atrophy may represent a cornerstone of imaging diagnosis in LOTS.[32] The presence of brainstem neuropathological abnormalities has been variable across limited pathological studies.[4,6,7] Cerebral atrophy was infrequently reported in both groups and suggests limited cortical involvement, which is also echoed by neuropathological reports.[4,6]

We assessed potential differentiating imaging features based on clinical characteristics. There was no significant association between age of onset and the presence of cerebellar atrophy, while the severity of reported atrophy was expectedly associated with longer disease duration.

We found clinical differences between LOTS and LOSD with and without cerebellar atrophy. Rates of ataxia in LOTS patients both with and without cerebellar atrophy were similar. In contrast, LOSD patients with cerebellar atrophy were much more likely to have reported clinical ataxia compared to those without cerebellar atrophy. This difference may suggest that LOTS patients have cerebellar pathology regardless of the presence of obvious cerebellar atrophy on imaging, whereas in LOSD, cerebellar symptoms tend to co-occur with the presence of cerebellar atrophy only. The characteristic stuttering speech[18] is a common feature of LOGG (particularly LOTS), and may be related to the distribution and degree of cerebellar pathology. In comparison, UMN features were more common in LOSD with cerebellar atrophy but not in LOTS. This may suggest that corticospinal involvement is more prevalent in LOSD. Of note, involvement of the spinocerebellar pathways has been reported in LOTS,[4] suggesting that assessing atrophy alone may underestimate cerebellar involvement.

Our findings support the hypothesis that in LOSD there may be a more frequent neuromuscular subtype, which is non-ataxic and associated with normal imaging.[20] The differences in symptoms associated with an ataxic presentation in LOTS versus LOSD (speech in LOTS and cognitive symptoms in LOSD), may be related to differential involvement of the motor or cognitive cerebellum.[33] Interestingly, HEXA is more highly expressed in the cerebral cortex compared to the cerebellum,[34] potentially making the cerebellum more vulnerable to loss of function mutations in this region. To test this hypothesis, more detailed studies assessing neuroimaging and correlation with gene expression are needed.

Regression analyses indicated independent predictors of LOTS versus LOSD were the presence of psychosis/bipolar symptoms, lack of swallowing problems and the presence of cerebellar atrophy (and when present, more severe cerebellar atrophy). In addition, a lower age of onset (highly significant on univariate testing) and clinical tremor were marginally significant but were felt sufficiently relevant to be included, particularly given the comparative limited sample size in LOSD. Adding to these, brainstem atrophy was only present in LOTS and is another key predictor, although its rarity precluded reaching significance on regression analysis.

We acknowledge limitations to our study. Firstly, from a semantic aspect, we defined late-onset as symptom onset on or after age 10, or having been clinically assessed at least once at age ≥ 18. This was necessary, given the lack of a consistent age definition for LOGG. Although our definition may have resulted in including some juvenile cases who survived into adulthood, this likely only involved very few cases. Age of onset was only reported as described in the cases and may be biased from retrospective assessment but was unavoidable given the reliance on the accuracy of the reported literature. Of a fundamental nature, out of necessity and by the nature of our scoping review, we assessed reports of imaging in LOGG patients, containing unavoidable downsides, including information bias from lack of accurate documentation, lack of granularity of descriptions of cerebellar atrophy severity, or authors potentially neglecting to mention relevant imaging features that were present. We did not report our own impression of published imaging in figures (few and not always representative sequences were included), to ensure consistency. Additionally, given the rarity of LOGG, it is also unclear how many of the patients described are unique, given possible overlap in the cases and series presented. When there was documentation of shared patients between studies, we were meticulous in only including patients once. Ethnicity was only defined by what was described by the authors. Most LOTS patients carry one common allele p.G269S as part of a compound heterozygous pair or homozygous. This variant is regarded as an "Ashkenazi Jewish" mutation. However, as most patients are unaware of their ancestry, this influence of ethnicity may be unrecorded.[35] An ascertainment bias was that only English language publications were included. The described phenotypes, are not necessarily exclusive, given clinical heterogeneity and clinical evolution over time. The small sample size (particularly in LOSD) likely influenced results. Distinguishing between specific genotypic differences was outside of the scope of the study.

These data suggest that there are significant differences in symptomatology, disease course, and imaging findings between LOTS and LOSD. LOTS patients had an earlier age of onset and were more likely to have tremor, ataxia, and psychosis/bipolar symptoms, had more frequent cerebellar atrophy on imaging, and when present, more severe cerebellar atrophy. In comparison, LOSD has a different presentation, with a more common neuromuscular phenotype, associated with normal imaging and, while infrequent, more common swallowing problems. These data have implications for clinical care and management in the two diseases and suggests that data from LOTS and LOSD should ideally be considered individually in secondary analyses in clinical trials.[36] However, the reality of an ultra-rare disease may necessitate being included en masse or resorting to N of 1 trials.[37,38]

Author Contributions

Ms. Godbole, Dr. Haxton, Ms. Rowe, Dr. Stephen: First draft of manuscript. Dr. Stephen: Study concept and design. Ms. Godbole, Dr. Haxton, Dr. Stephen: acquisition of data. Dr. Stephen, Ms. Rowe, Dr. Schmahmann, Dr. Locascio, Dr. Eichler, Dr. Ratai: analysis and interpretation. Ms. Godbole, Dr. Haxton, Dr. Schmahmann, Dr. Locascio, Dr. Eichler, Dr. Stephen, Ms. Rowe, Dr. Ratai: critical revision of the manuscript for important intellectual content.

Disclosures

Ms. Godbole, Dr. Haxton, Ms. Rowe, Dr. Locascio, Dr. Schmahmann, Dr. Eichler, Dr. Ratai, and Dr. Stephen report no conflicts of interest relevant to the manuscript. Dr. Ratai is a member of the advisory board at BrainSpec.

Funding Information

This study was supported by the National Institutes of Health/National Institute of Neurological Disorders and Stroke K23NS118045 (CDS). Study was not industry sponsored.

Financial Disclosures for Authors (for the Preceding 24 Months)

Ms. Rowe is currently employed by Cognito Therapeutics.

Dr. Ratai is a member of the advisory board at BrainSpec.

Dr. Eichler Is the Founder of SwanBio Therapeutics and has been reimbursed for consulting from SwanBio Therapeutics. He has received honoraria from the American Neurological Association and UpToDate. His institution has received funding for him conducting clinical trials from Ionis Therapeutics, Bluebird Bio, Sanofi-Genzyme, and Minoryx Therapeutics. He has received grant support from the National Institutes of Health U54NS115052 and ELA International 2019-012I2.

Dr. Stephen has provided scientific advisory for SwanBio Therapeutics and his institution has received research funding from Sanofi-Genzyme for a study of video oculography in late-onset GM2 gangliosidosis. His institution has received financial support from Encora Therapeutics, Sanofi-Genzyme, Biogen and Biohaven for the conduct of clinical trials. He has received honoraria from the International Parkinson and Movement Disorders Society, the American Academy of Neurology/Continuum and Oakstone CME for the production of educational material. He has received grant support from the National Institutes of Health K23NS118045.

Ms. Godbole, Dr. Haxton, Dr. Locascio and Dr. Ratai report no financial disclosures.

Data Availability Statement

The data are comprised of a scoping review of the literature and hence the original data sources are available electronically. Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator for purposes of replicating procedures and results.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1 Supporting Information.

